PHASE I/II STUDY OF UMBRALISIB, UBLITUXIMAB, AND PEMBROLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND RICHTER'S TRANSFORMATION: 5-YEAR FOLLOW-UP

Lindsey E. Roeker, MD[1], Mazyar Shadman, MD, MPH[2], Jakub Svoboda, MD[3], Eline T. Luning Prak, MD, PhD[4], Stephen J. Schuster, MD, PhD[3], Patricia Y. Tsao, MD, PhD[4], Colleen Dorsey, BSN, RN[1], Gail Panton, BSN, RN[1], Sunita D. Nasta, MD, FACP[3], Daniel J. Landsburg, MD[3], Beth Morrigan[2], Jill Elwell[2], Kaitlin Kennard, RN, BSN[3], Andrew D. Zelenetz, MD, PhD[1], Michelle Purdom[5], Dana Paskalis[5], Peter Sportelli[5], Hari P. Miskin[5], Michael S. Weiss[5], Anthony R. Mato, MD, MSCE[3]

[1]CLL Program, Leukemia Service, Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [4]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia PA; [5]TG Therapeutics Inc. New York, NY

For questions contact: roekerl@mskcc.org

Background / Rationale: PD-1/PD-L1 axis

- Pre-clinical data support a major role for the PD-1 and PD-L1/PD-L2 axis in mediating immune evasion in CLL. However, there is a disconnect between promising preclinical data and clinical data with anti-PD-1 monotherapy.
- A key interaction exists between PI3K signaling and immune checkpoint surveillance by which inhibition of PI3K decreases PD-L1 tumor expression, suggesting potential synergistic activity with PD-1 + PI3K blockade.

Study	Efficacy
CLL (Mayo), n=16	ORR 0%, PFS 2.4 months, OS 11.2 months
RT (Mayo), n=9	ORR 44%, PFS 5.4 months, OS 10.7 months
Real world data (OSU), n=10	90% failure rate in RT, OS 2 months

Grzywnowicz et al., *PLOS* 2012. Brusa et al., *Haem* 2012. Palma et al., *Haem* 2017. Ringelstein-Harlev et al. *Blood* 2014. Ding et al., *Blood* 2017. Rogers et al., *BJH* 2018.

Umbralisib + Ublituximab ("U2")

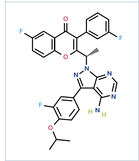
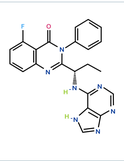
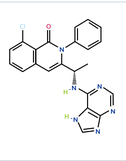
Umbralisib: an oral, once-daily, novel, inhibitor of PI3Kδ and casein kinase-1epsilon (CK1ε)

- Phase 2/3 dose: 800 mg QD

Ublituximab: glycoengineered anti-CD20 monoclonal antibody

- Enhanced ADCC compared to rituximab

[1]Burris et al., *Lancet Oncology* 2018

	Umbralisib[1]	Idelalisib[1]	Duvelisib[1]
			

Isoform	K_d (nM)		
PI3kα	>10000	600	40
PI3Kβ	>10000	19	0.89
PI3Kγ	1400	9.1	0.21
PI3Kδ	6.2	1.2	0.047
CK1ε	180	>30,000	>30,000

Rationale

Umbralisib was selected due to preclinical data showing minimal effect on T-regs and clinical experience showing favorable toxicity profile

Study Design

Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety & efficacy of U2 + pembrolizumab in patients with R/R CLL and RT (NCT02535286)

- **Cohort 1:** Pembrolizumab 100 mg
- **Cohort 2:** Pembrolizumab 200 mg

Correlative studies: Peripheral blood and/or bone marrow samples were collected at screening, during cycle 2 and cycle 6

Study Objectives

Primary Objective

- To determine the safety of U2 + pembro in CLL and RT patients

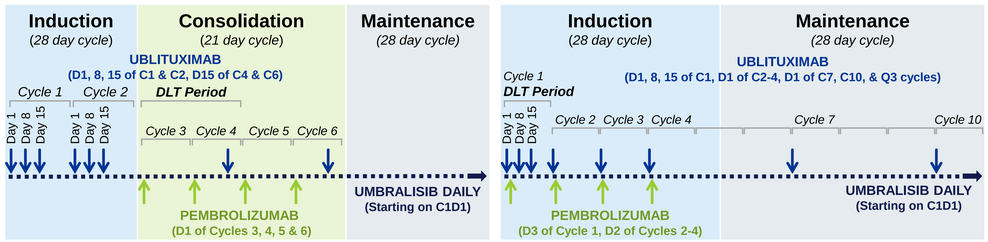
Key Secondary Objectives

- To evaluate efficacy (ORR, PFS) – iwCLL (2008) & Cheson (2007)
- To describe the immunophenotypic profiles of B and T cells

Key Eligibility Criteria

- CLL: progressed on at least one prior therapy
  - Mid-study amendment required CLL pts to be BTK refractory (PD within 6 mos of prior BTK)
- RT: chemo-immunotherapy refractory or not eligible for high-dose chemo
- No limit on # of prior therapy treatment regimens
- ANC > 750/μL, platelet count > 40,000/μL
- Prior exposure to PD-1 or PI3K inhibitor was NOT an exclusion

Treatment Schedule



- Efficacy assessed at the end of Cycles 2, 6 & 12. After Month 12, efficacy is assessed per investigator discretion.
- C1D1 dose split between D1 and D2

- Efficacy assessed at the end of Cycles 2 & 4 and Q3 cycles thereafter until Month 12. After Month 12, efficacy assessed per investigator discretion.
- Cycle 1D1 dose split between D1 and D2

Results

Demographics

Chronic Lymphocytic Leukemia

Evaluable for Safety & Efficacy, n	CLL, N=11
Median Age, years (range)	70 (60 - 81)
Male/Female	7 / 4
ECOG, 0/1/2	5 / 6 / 0
Prior Therapy Regimens, median (range)	1 (1 – 4)
Prior BTK (ibrutinib or acalabrutinib), n (%)	7 (64%)
Refractory to prior BTK	6/7 (86%)
Refractory to immediate prior therapy, n (%)	8 (73%)
At least 1 high risk feature	8 (73%)
≥2 high risk features, n (%)	6 (55%)
17p del/TP53 mutated, n (%)	3 (27%)
Complex Karyotype, n (%)	5 (45%)
NOTCH1/ATM/SF3B1mut, n (%)	5 (45%)
IGHV Unmutated, % (n/N)	57% (4/7)
Bulky Disease, n (%)	7 (64%)

Richter's Transformation

Evaluable for Safety, n	RT, N=9
Evaluable for Efficacy†, n	8
Median Age, years (range)	66 (53 - 73)
Male/Female	6 / 3
ECOG, 0/1/2	3 / 5 / 1
Prior Therapy Regimens, median (range)	5 (1 – 9)
Prior ibrutinib	8 (89%)
Refractory to prior ibrutinib	8/8 (100%)
Prior Chemo Regimen	9 (100%)
Prior idelalisib + rituximab	2 (22%)
Prior venetoclax	3 (33%)
Prior CAR-T / Allo Transplant	3 (33%)
Refractory to immediate prior therapy	8 (89%)
Bulky Disease, n (%)	8 (89%)

†1 RT patient not evaluable – treated on CLL regimen

Disposition and Safety

Enrollment by Cohort

Pembro Dose	CLL	RT	Total
100 mg	5	4	9
200 mg	6	5	11

- 1 DLT at 200 mg pembro dose (transient elevated LFT - resolved); MTD not reached
- Grade 3/4 LFT elevations occurred in 4 patient (20%)
- No Grade 3/4 diarrhea
  - 1 patient had grade 5 colitis secondary to c-diff, unrelated to therapy
- Median follow-up for all patients: 48 mos (54 mos for CLL cohort)
- No patient had their pembro dose reduced while 4 patients had their umbralisib dose reduced[§]

‡Includes neutropenia & neutrophil count decreased MedDRA preferred terms
[§]AEs leading to umbralisib dose reductions include: asthenia/fatigue (G3, 1 patient), neutrophil count decrease (G3, 1 patient), ALT increase (G2, 1 patient), and headache (G2, 1 patient)

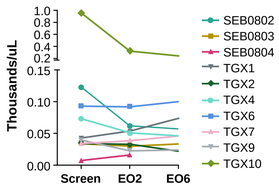
Adverse Events for (All Causality) >20% (N=20)

	All Grades		Grade ≥3	
	N	%	N	%
Neutropenia‡	12	60.0%	9	45.0%
Pyrexia	10	50.0%		
Diarrhea	10	50.0%		
Nausea	9	45.0%	1	5.0%
Chills	9	45.0%		
Cough	9	45.0%		
Fatigue	9	45.0%	1	5.0%
Thrombocytopenia	8	40.0%	3	15.0%
Decreased appetite	8	40.0%		
Headache	8	40.0%		
Infusion related reaction	7	35.0%		
Oedema peripheral	6	30.0%		
Alkaline phos increase	6	30.0%		
Leukopenia	6	30.0%	2	10.0%
Dizziness	6	30.0%		
Nasal congestion	6	30.0%		
Contusion	5	25.0%		
Myalgia	5	25.0%		
Oral candidiasis	5	25.0%		
Anemia	5	25.0%	1	5.0%
Pruritus	5	25.0%		
ALT increase	5	25.0%	3	15.0%
Insomnia	5	25.0%		
Vomiting	5	25.0%		

Correlatives: T-reg Population

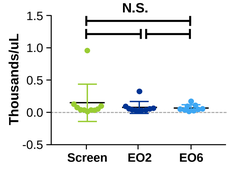
Circulating FoxP3+ CD4+ T cell levels do not change significantly in CLL study patients

FoxP3+ CD_4 Cells vs. Time



FoxP3 Column Analysis

(CD3+ CD4+ FoxP3+ Lymphs, PB)

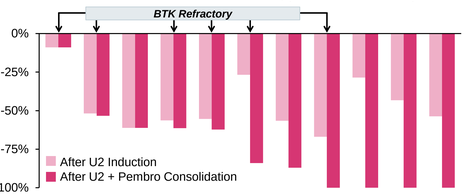


Efficacy: ORR in CLL

Group	CR N (%)	PR N (%)	SD N (%)	ORR N (%)
CLL N=11	1 (9%)	9 (82%)	1 (9%)	10 (91%)

BTK Refractory CLL

- **ORR: 83% (5/6)**
- 80% of BTK Refractory responders (4/5) achieved response after U2 Induction, prior to addition of pembro

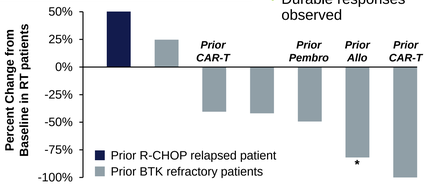


Efficacy: ORR in RT

Group	CR N (%)	PR N (%)	SD N (%)	ORR N (%)
RT N=8	2 (25%)	—	3 (38%)	2 (25%)

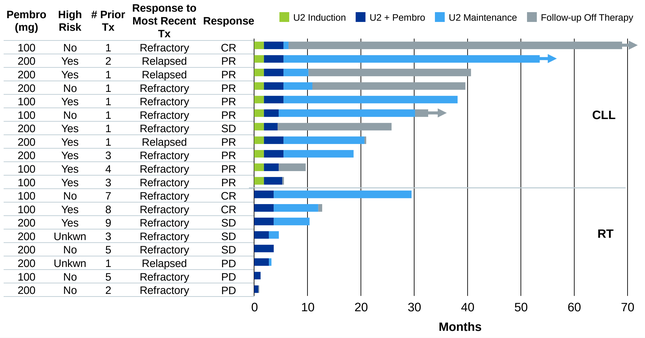
Heavily refractory Richter's

- 7/8 BTK Refractory
- Durable responses observed



*PET negative
Note: Waterfall plot includes all patients with at least one evaluable post-baseline scan

Efficacy & Tolerability: Duration of Exposure



Case Study: RT Patient

62 yo Male

Prior Treatment History for CLL:

- **2008:** PCR
- **2011:** BR
- **2013:** FCR
- **2013:** Ofatumumab + Fludara + Cyclophosphamide
- **2014:** Alemtuzumab
- **2014:** Allo Transplant

Prior Treatment for RT:

- **Nov 2014:** R-CHOP + Ibrutinib
  - PD while on Ibrutinib in 2017
  - Target Lesion SPD = 45 cm

Started U2 + Pembro Cohort 1 - 100 mg

- End of Cycle 2: 76%↓ - PR
- End of Cycle 5: 78%↓ - PR
- End of Cycle 8: Complete Response
  - PET-negative by Lugano Criteria (Cheson 2014)
- Tolerated U2 + Pembro well
  - 1 G3 event of Hypophosphatemia (possibly related)
  - 1 G3 event of Hyperglycemia (not related)
  - No umbralisib dose modifications required

Subject was in CR for 29.5 mos

Conclusions

Triplet combination of umbralisib + ublituximab ("U2") + pembrolizumab was well tolerated

- Immune mediated toxicities were not increased above what would be expected with either umbralisib or pembrolizumab alone

Responses were durable in BTK refractory, high-risk pts, including two durable CRs in RT pts

- Final efficacy analysis suggests that CLL pts who achieve less than CR with a checkpoint inhibitor-containing regimen can achieve durable remissions and that time-limited schedules should be explored

Maintenance of T-regs throughout therapy may explain limited autoimmune sequelae

Acknowledgements

- Thank you to the patients and their families for their participation.